PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/014435	17.12.2004	17.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61K38/17, C07K16/28, A61P19/00

Applicant
UTKU, Nalan

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Filed: Herewith (as §371 national stage of PCT/EP2004/014435)
Exhibit 8

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1 in part and 20 with respect to industrial applicability

because:

☒ the said international application, or the said claims Nos. 20 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 1 in part

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	2-3,12,15-20
	No:	Claims	1,4-11,13,14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-20
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Re Item II

Priority

It should be noted that the documents D4-D5 indicated in the search report as 'PX documents' have not been taken into consideration for the evaluation of novelty and inventive step, since the priority of the present application had to be assumed as valid (see also Official Journal EPO, 11/2001, page 539-542, especially item 13).

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

I. Claim 20 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

II. Present claim 1 relate to a product defined by reference to a desirable characteristic or property, namely an agent that selectively modulates cross-linking of biliary glycoprotein polypeptides. The claims cover all products having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such product. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to anti-CEACAM1 antibodies, CEACAM1 fragments, CEACAM1 fragments fused to an immunoglobulin or to a Fc fragment.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; 2003, IIJIMA HIDEKI ET AL: "SPECIFIC REGULATION OF T HELPER-1 MEDIATED MURINE COLITIS BY CEACAM1 ." XP002343170 Database accession no. PREV200400032288

D2: SZEKANECZ ZOLTAN ET AL: "Increased synovial expression of the adhesion molecules CD66a, CD66b, and CD31 in rheumatoid and osteoarthritis" CLINICAL IMMUNOLOGY AND IMMUNOPATHOLOGY, vol. 76, no. 2, 1995, pages 180-186, XP002343166 ISSN: 0090-1229

D3: WO 99/52552 A (BRIGHAM & WOMEN'S HOSPITAL, INC) 21 October 1999 (1999-10-21)

Novelty

I. The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1,4-11,13 and 14 is not new in the sense of Article 33(2) PCT.

The document D1 discloses (see abstract) the interaction of the CEACAM1-specific monoclonal antibody, CC1, a CEACAM-Fc fusion protein and the MHV spike protein with CEACAM1 expressed in transfected Jurkat cells, and shows how the CEACAM-Fc fusion protein is able to block the development of oxazolone-induced colitis in mice.

II. The subject-matter of claims 2,3,12 and 15-20 differs from this D1 in that the claimed fusion protein of the present application consists of a CECAM1's fragment (aa sequence from position 1-228 of SEQ.ID.N.2), or a fragment thereof, and the hinge CH2-CH3 region of the Fc portion of an immunoglobulin used to treat multiple sclerosis and rheumatoid arthritis, whereas in D1 CECAM1 (in its whole length) is fused to an Fc

immunoglobulin fragment and used to treat oxazolone-induced colitis.

Thus, the subject-matter of claims 2,3,12 and 15-20 is novel.

Inventive step

The problem to be solved by the present application is the provision of an 'agent' that selectively modulates crosslinking of biliary glycoprotein peptides to treat inflammatory diseases.

The proposed solution is the provision of a fusion protein comprising a fragment of a biliary glycoprotein and a fragment of an immunoglobulin.

The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-20 does not involve an inventive step in the sense of Article 33(3) PCT for the following reasons:

D1 shows (see abstract) a CEACAM-Fc fusion protein which is able to block the development of oxazolone-induced colitis in mice. The homophyllic or heterophyllic ligation of the CEACAM1 N-domain specifically stimulates an inhibitory pathway in T cells and modifies the Th1-associated immunopathology.

It is known from prior art documents that CEACAM1 (CD66a) is increasedly expressed in macrophages present in the diseased synovial tissue of patients suffering from rheumatoid arthritis and osteoarthritis, see D2 (abstract, page 180, left-hand column, first paragraph to page 181, left-hand column, 1st paragraph; page 181, right-hand column, 4th paragraph and figure 2). Moreover, D3 discloses Fc fusion proteins containing the N-domain of CD66a (CEACAM1), the NA1B1 domain of CD66a or NA1B1A2 domain of CD66a (see page 2, lines 25-31; page 3, lines 10-18; page 21, lines 27-32; examples 3-6 and figure 3) which have incorporated the hinge CH2 and CH3 domains of the human Fc fragment of IgG1.

In view of the above paragraph, the skilled person would regard it a normal design procedure to combine all the features set out in claims 2,3,12,15-20 in order to solve the problem posed. Therefore, it is concluded that the subject-matter of claims 1-20 does not involve an inventive step.

Industrial applicability

For the assessment of the present claim 20 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI

Certain documents cited

D4: IIJIMA HIDEKI ET AL: "Specific regulation of T helper cell 1-mediated murine colitis by CEACAM1." JOURNAL OF EXPERIMENTAL MEDICINE, vol. 199, no. 4, 16 February 2004 (2004-02-16), pages 471-482, XP002343167 ISSN: 0022-1007

D5: CHEN DAOHONG ET AL: "Carcinoembryonic antigen-related cellular adhesion molecule 1 isoforms alternatively inhibit and costimulate human T cell function." JOURNAL OF IMMUNOLOGY, vol. 172, no. 6, 15 March 2004 (2004-03-15), pages 3535-3543, XP002343168 ISSN: 0022-1767